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EXAMINER	
OLSON, ERIC	
ART UNIT	**PAPER NUMBER**
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/657,508	ZOMER ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,17,19,20 and 22-30* is/are pending in the application.

4a) Of the above claim(s) *1-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *13-15,17,19,20 and 22-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted May 3, 2007 wherein claims 13-15, 17, 19, 20, and 22-25 are amended, claims 16, 18, and 21 are cancelled, and new claims 26-30 are introduced. This application was filed September 8, 2003, and makes no priority claims.

Claims 1-15, 17, 19, 20, and 22-30 are pending in this application.

Claims 13-15, 17, 19, 20, and 22-30 as amended are examined on the merits herein.

The terminal disclaimers filed on April 2, 2007 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US patents 6645946, 6982255, and 7012068, have been reviewed and are accepted. The terminal disclaimers have been recorded.

Applicant's amendment, submitted May 3, 2007, with respect to the objection to claims 14-16, 23, and 25 for containing abbreviations without any description of the full names of said compounds, has been fully considered and found to be persuasive to remove the objection as the claims have been amended to recite the full names of these species. Therefore the objection is withdrawn.

Applicant's amendment, submitted May 3, 2007, with respect to the rejection of instant claims 13-25 under 35 USC 112, first paragraph, for lacking

enablement for all possible cancers, has been fully considered and found to be persuasive to remove the rejection as the claims are no longer drawn to a method of treating cancer. Therefore the rejection is withdrawn.

Applicant's argument, submitted May 3, 2007, with respect to the rejection of instant claims 19-25 under 35 USC 112, second paragraph, for not reciting a specific ratio of active agents, has been fully considered and found to be persuasive to remove the rejection as the specification provides examples of suitable ratios. Therefore the rejection is withdrawn.

Applicant's terminal disclaimer, submitted May 3, 2007, with respect to the rejection of instant claims 13-22 under the doctrine of obviousness-type double patenting, for claiming the same invention as US patents 6645946, 7012068, and 6982255, has been fully considered and found to be persuasive to remove the rejections. Therefore the rejections are withdrawn.

The following new grounds of rejection are introduced:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-27 recite the limitation "wherein the chemotherapeutic agent is selected from the group consisting of...". There is insufficient antecedent basis for this limitation in the claim. Specifically, the base claim 22 specifically limits

the chemotherapeutic agents to proteinous chemotherapeutic agents, while the dependent claims recite small molecule non-proteinous chemotherapeutic agents. Therefore the dependent claims lack antecedent basis in the base claim.

Claims 17 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims are drawn to a therapeutic method, yet they include the limitation that the method comprises leucovorin. A method comprises method steps, not compounds. It is not clear what role the leucovorin plays in the method how it is to be used. Therefore the claims are indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 19, 20, 22, 28, and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method involving certain specific chemotherapeutic agents such as fluorouracil, does not reasonably provide enablement for any possible chemotherapeutic agent whatsoever. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a therapeutic method comprising administering two compounds, one of which is a chemotherapeutic agent.

The state of the prior art: The prior art discloses a wide variety of chemotherapeutic agents, including various small molecules, proteins, and nucleosides, for example. The work by a wide variety of methods, such as inhibiting various enzymes or damaging DNA, for example. The prior art also discloses guar gum and galactomannan as pharmaceutical excipients that are used to improve the delivery of a wide variety of different therapeutic agents, usually orally.

The prior art does not disclose the full scope of all possible chemotherapeutic agents, or a way to discover and produce all such agents.

The relative skill of those in the art: The relative level of skill in the art is high.

The predictability or unpredictability of the art: The treatment of cancer is highly unpredictable. Cancer cells comprise many different biochemical pathways and molecular targets, any of which is a potential target for chemotherapy. There are many different strategies which can be pursued in an attempt to produce novel chemotherapeutic agents.

Furthermore, the class of chemotherapeutic agents includes a wide variety of diverse chemical structures. Synthesis of novel compounds is a complex process of trial and error which is necessary in order to develop a workable synthetic scheme for any novel compound. Therefore many compounds are difficult to obtain. Note that merely sampling a somewhat diverse chemical library built from a known scaffold, as is the case with typical drug screening programs, is not the same as testing every possible compound for a given activity, as would be required to find **every** compound with that activity.

The Breadth of the claims: The claimed invention is very broad, encompassing any compound with utility as a cancer chemotherapeutic, namely any substance whatsoever that can be administered so as to inhibit or kill cancer cells without killing the host.

The amount of direction or guidance presented: The claimed specific galactomannans are described and disclosed to be obtainable from guar. A wide variety of different chemotherapeutic agents are listed as being enhanced by this galactomannan. No guidance is given that would enable one skilled in the art to

discover new chemotherapeutic agents, much less all possible new chemotherapeutic agents.

The presence or absence of working examples: The specification discloses a number of tests showing improvement in the efficacy and toxicity of 5-FU (5-fluorouracil) when administered with the claimed galactomannan.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the discovery of completely novel chemotherapeutic agents. See MPEP 2164.

The quantity of experimentation necessary: One of ordinary skill in the art, in order to practice the claimed invention with the full range of chemotherapeutic agents beyond the meager number disclosed in the specification would be required to test potential compounds *in vivo* to determine whether a particular compound is useful as a chemotherapy agent. According to the 2006 Chemical Abstracts catalog, (Reference included with PTO-892) The Chemical Abstracts Registry contains entries for approximately 26 million compounds, all of which are potentially included in the claimed invention if they happen to have anticancer activity. For most compounds, it is unknown whether they are or are not useful for chemotherapy. Gathering this data for every compound known to man would involve *in vitro* screening of an enormous diversity of chemical compounds for anticancer activity, as well as *in vivo* testing of compounds having this activity involving either human or animal subjects to determine therapeutic utility. *In vitro* testing requires that the compounds to be tested be synthesized and subjected to an appropriate screening method. As described earlier, synthesis of diverse

chemical structures requires novel and unpredictable experimentation in order to develop suitable synthetic methods. *In vivo* animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Human tests impose even greater ethical and regulatory burdens, as well as additional difficulty locating subjects. Because of the unpredictability of the art and the lack of comprehensive working examples covering any significant portion of the total number of potential chemotherapeutics, these animal experiments would need to be repeated hundreds of times, and involve the maintenance, killing, dissection, and disposal of thousands of experimental animals, to establish the activity or lack thereof of every possible chemotherapeutic, thus presenting an a burden of undue experimentation to anyone practicing the invention with the full range of chemotherapeutic agents claimed.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the unpredictability of the art, Applicants fail to

provide information sufficient to practice the claimed invention for all possible chemotherapeutic agents.

Claim 28 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a therapeutic method comprising co-administering two or more therapeutic agents.

The state of the prior art: Leucovorin is known in the prior art to be useful in combination with certain chemotherapeutic agents such as 5-fluorouracil or methotrexate, to either improve the efficacy of the chemotherapeutic or to reduce

its toxicity. It is not known to be a useful chemotherapeutic in its own right, in the absence of a primary agent, or to be useful for improving the effects of proteinous agents such as cytokines.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: The prediction of drug-drug interactions is highly unpredictable. Avery's Drug Therapy, 3rd edition, (Reference included with PTO-892) states that, "Pharmacokinetic interactions observed *in vitro* or in animals will not necessarily occur in man," "Interactions will not necessarily occur in all patients receiving a given combination of drugs known to have a potential for interaction in man," and "Many clinically important interactions, especially those of a pharmacokinetic nature, depend on a variety of factors additional to the drugs given." (Chapter VIII, p. 255, Synopsis of Important Principles, no. 4-6) Although the cited reference is concerned primarily with negative drug-drug interactions, positive interactions are expected to act in much the same manner.

The Breadth of the claims: The claimed invention comprises co-administering any proteinous anticancer agent with leucovorin. This scope includes cytokines and monoclonal antibodies, for example.

The amount of direction or guidance presented: The specification describes leucovorin as being an enhancer that can be co-administered with chemotherapeutics. However, it is solely described as being useful in combination with 5-fluorouracil, not with cytokines or other proteins.

The presence or absence of working examples: The only working examples of leucovorin-comprising therapies involve coadministration with 5-fluorouracil, not with cytokines or other proteins.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as drug-drug interactions. See MPEP 2164.

The quantity of experimentation necessary: There is no reason to believe that there is any therapeutic benefit to coadministering leucovorin with cytokines, or with any other proteinous chemotherapeutic. Its positive effect on chemotherapeutic regimens is due to its enhancement of the effect of fluorouracil and its rescue of the toxicity of methotrexate and similar agents. Simply combining leucovorin with any given proteinous active agent is not expected to yield a benefit. Therefore one skilled in the art, in developing such a therapy, would be starting from scratch, developing an unpredictable and untried therapy, with no expectation of success. This process would reasonably be considered to be an undue and unpredictable experimental burden.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the state of the art and the lack of guidance or working examples, Applicants fail

to provide information sufficient to practice the claimed invention for combinations of leucovorin and proteinous chemotherapeutic agents.

Claim 28 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant's amendment submitted May 3, 2007 with respect to the aforementioned claims has been fully considered and but is deemed to insert **new matter** into the claims since the specification as originally filed does not provide support for a method comprising administering a proteinous chemotherapeutic agent in combination with leucovorin. As the instant specification as filed contains no description of such a combination, or of any activity of leucovorin that does not depend on coadministration with the nucleoside 5-fluorouracil, the specification as originally filed does not provide support for the subject matter of instant claim 28. See *in re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 13-15, and 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al. (US patent 6413494, cited in PTO-1449) Lee et al. discloses a composition and pharmaceutical dosage form for delivering an orally administered drug specifically to the colon, thereby improving its biodistribution in the body. (column 4, lines 30-36) Drugs that can be administered in this manner include antineoplastics. (column 6, line 35) In particular, drugs for treating colon cancer can be specifically administered to the colon using these formulations (column 8, lines 52-55) for example, methotrexate or 5-fluorouracil. (column 9, line 14) The dosage form also comprises galactomannan, (column 7, lines 16-22) such as guar gum. (column 7, lines 38-40) Guar gum is a galactomannan having the characteristics of the claimed invention, as disclosed on p. 24 of the instant specification. Therefore administering the fluorouracil-containing compositions of Lee et al. is reasonably considered to be a method comprising the same steps as, and thus anticipating, the clamed invention.

Claims 13-15, 22, 25-27, and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Simard et al. (US patent application 10/499313, published as 20060057131, cited in PTO-892) Simard et al. discloses a biodegradable and

non-toxic malleable protein matrix for delivering pharmaceuticals. (p. 2, paragraphs 0020-0023) Also included in the matrix is a polysaccharide which can be a galactomannan, particularly guar gum. (p. 3, lines 0045-0047) This matrix can be used in drug tablets to produce a tablet that hydrates slowly and protects the incorporated agent while passing through the stomach. (p. 7, paragraph 0108) This effect is reasonably considered to be an effect of improving biodistribution of a drug as recited by the instant claims. A wide variety of bioactive agents can be used in the disclosed composition, including chemotherapeutic drugs and therapeutic proteins such as interferons, interleukins, and cytokines. (p. 10, paragraphs 0132-0133) In one example, 5-fluorouracil was prepared with the aforementioned protein/polysaccharide matrix and administered to mice bearing colon cancer cells, and found to have an improved therapeutic index. (p. 20, paragraph 0197) This therapeutic method is reasonably considered to be a method comprising administering a chemotherapeutic agent and the disclosed galactomannan according to the instant claims, thus anticipating the claimed invention.

Claims 13, 22-24, 29, and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Bøving et al. (PCT international publication WO2004024183, reference included with PTO-892) Bøving et al. discloses a method for treating obesity and other diseases comprising downregulating ghrelin by immunizing against autologous ghrelin. (p. 6, lines 16-30) The vaccine compositions administered in this method can include adjuvants, such as interleukin-2 or

interleukin-12. (p. 20, lines 7-12) The ghrelin antigen can be coupled to a polyhydroxypolymer. (p. 44, lines 25-34) Preferred polyhydroxypolymers include guar, which is a galactomannan having the characteristics of the claimed invention, as disclosed on p. 24 of the instant specification. (p. 46, lines 1-5) Although Bøving et al. does not explicitly disclose that the interleukins are proteinous chemotherapeutic agents, this property is inherent to the recited interleukins. This method comprises the same steps as the claimed invention, administering the same compounds to a subject. See *Ex parte Novitski* 26 USPQ 2d 1389, 1391 (Bd. Pat. App. & Int. 1993). Note that the claiming of a new use, new function, or unknown property which is inherently present in the prior art does not make the claim patentable. See *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). See also *Eli Lilly and Co. v. Barr Laboratories Inc.* 251 F3c. 955; 58 USPQ2d 1869-1881 (Fed. Cir. 2001) with regard to inherency as it relates to the claimed invention herein. Therefore Bøving et al. anticipates the claimed invention.

Claims 13-15, 19, 20, an 25-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Klyosov et al. (US patent 6645946, reference of record in previous action) Klyosov et al. discloses a method for treating cancer comprising administering a chemotherapeutic agent and a galactomannan. (column 2, lines 25-28) The galactomannan used can have a ratio of 2.0-3.0 mannose to 0.5-1.5 galactose or particularly 2.6 galactose to 1.5 mannose, which is the same as the ratio of 1.7:1.0 of the galactomannan used in the claimed invention, as disclosed

on p. 24 of the instant specification. (column 2, lines 40-48) In one embodiment the chemotherapeutic agent us 5-fluorouracil. (column 2, lines 56-58) In one embodiment the cancer is colon cancer. (column 2, lines 59-65) The preferred galactomannan has a structure that is the same as that of the claimed invention disclosed on p. 24 of the instant specification. (column 6, lines 1-5) The galactomannan and the therapeutic agent can be administered in a ratio of 1:1.9 of galactomannan to fluorouracil. (column 5, lines 31-39) Therefore the invention disclosed by Klysov et al. is the same as that of the claimed invention, and anticipates the claimed invention.

The applied reference has a common assignee and one common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (US patent 6413494, cited in PTO-1449) The disclosure of Lee et al. is discussed above. Lee et al. does not disclose a ratio of galactomannan and chemotherapeutic agent in the ranges disclosed in instant claims 19 and 20.

It would have been obvious to one of ordinary skill in the art at the time of the invention to formulate the compositions of Lee et al. having a ratio of ingredients in the ranges of instant claims 19 and 20. A person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. In the absence of unexpected properties not predicted by the prior art, this is the product not of innovation but of ordinary skill and common sense.

Therefore the invention taken as a whole is *prima facie* obvious.

Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simard et al. (US patent application 10/499313, published as 20060057131, cited in PTO-892) The disclosure of Simard et al. is discussed above. Lee et al. does not disclose a ratio of galactomannan and chemotherapeutic agent in the ranges disclosed in instant claims 19 and 20.

It would have been obvious to one of ordinary skill in the art at the time of the invention to formulate the compositions of Simard et al. having a ratio of ingredients in the ranges of instant claims 19 and 20. A person of ordinary skill in the art has good reason to pursue the known options within his or her technical

grasp. In the absence of unexpected properties not predicted by the prior art, this is the product not of innovation but of ordinary skill and common sense.

Therefore the invention taken as a whole is *prima facie* obvious.

Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bøving et al. (PCT international publication WO2004024183, reference included with PTO-892) The disclosure of Bøving et al. is discussed above. Lee et al. does not disclose a ratio of galactomannan and chemotherapeutic agent in the ranges disclosed in instant claims 19 and 20.

It would have been obvious to one of ordinary skill in the art at the time of the invention to formulate the compositions of Bøving et al. having a ratio of ingredients in the ranges of instant claims 19 and 20. A person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. In the absence of unexpected properties not predicted by the prior art, this is the product not of innovation but of ordinary skill and common sense.

Therefore the invention taken as a whole is *prima facie* obvious.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (US patent 6413494, cited in PTO-1449) in view of Jakobsen et al. (Reference included with PTO-892) The disclosure of Lee et al. is discussed above. Lee et al. does not disclose a method further comprising administering leucovorin.

Jakobsen et al. discloses a study of different does intensities of 5-fluorouracil. (p. 526, left column, second paragraph) The patients treated had recurrent colorectal cancer. (p. 526, left column, third paragraph) All treatment groups received fluorouracil in combination with leucovorin. (p. 526, left column fourth paragraph, right column first paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to coadminister the fluorouracil-containing compositions of Lee et al. with leucovorin, to a patient having colon cancer. One of ordinary skill in the art would have been motivated to combine these two elements because Jakobsen et al. specifically discloses that 5-fluorouracil can be productively co-administered with leucovorin for treating colon cancer. One of ordinary skill in the art would reasonably have expected success because combining two elements known in the prior art to be useful for treating the same condition is well within the ordinary and routine level of skill in the art.

Therefore the invention taken as a whole is *prima facie* obvious.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Simard et al. (US patent application 10/499313, published as 20060057131, cited in PTO-892) in view of Jakobsen et al. (Reference included with PTO-892) The disclosure of Simard et al. is discussed above. Simard et al. does not disclose a method further comprising administering leucovorin.

Jakobsen et al. discloses a study of different does intensities of 5-fluorouracil. (p. 526, left column, second paragraph) The patients treated had

recurrent colorectal cancer. (p. 526, left column, third paragraph) All treatment groups received fluorouracil in combination with leucovorin. (p. 526, left column fourth paragraph, right column first paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to coadminister the fluorouracil-containing compositions of Simard et al. with leucovorin, to a patient having colon cancer. One of ordinary skill in the art would have been motivated to combine these two elements because Jakobsen et al. specifically discloses that 5-fluorouracil can be productively co-administered with leucovorin for treating colon cancer. One of ordinary skill in the art would reasonably have expected success because combining two elements known in the prior art to be useful for treating the same condition is well within the ordinary and routine level of skill in the art.

Therefore the invention taken as a whole is *prima facie* obvious.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (US patent 6413494, cited in PTO-1449) in view of Van den Bongard et al. (Reference included with PTO-892) The disclosure of Lee et al. is discussed above. Lee et al. does not disclose a method further comprising administering leucovorin.

Van den Bongard et al. discloses a case study of a patient receiving methotrexate with leucovorin rescue therapy. (p. 538, left column, fourth paragraph) The patient developed renal failure which was reversed by administration of escalated doses of leucovorin. (p. 538, right column,

paragraphs 2-3) Leucovorin is shown to be a useful rescue therapy for treating the toxicity of methotrexate.

It would have been obvious to one of ordinary skill in the art at the time of the invention to coadminister the methotrexate-containing compositions of Lee et al. with leucovorin, to a patient having cancer. One of ordinary skill in the art would have been motivated to combine these two elements because Van den Bongard et al. specifically discloses that leucovorin is useful for attenuating the toxicity of methotrexate. One of ordinary skill in the art would reasonably have expected success because combining two elements known in the prior art to be useful for treating the same condition is well within the ordinary and routine level of skill in the art.

Therefore the invention taken as a whole is *prima facie* obvious.

Claims 13-15, 19, 20, an 25-27 are rejected under 35 U.S.C. 103(a) as being obvious over Klyosov et al. (US patent 6645946, reference of record in previous action) The disclosure of Klysov et al. is discussed above. Klysov et al. does not disclose a method further comprising administering leucovorin. Jakobsen et al. discloses a study of different does intensities of 5-fluorouracil. (p. 526, left column, second paragraph) The patients treated had recurrent colorectal cancer. (p. 526, left column, third paragraph) All treatment groups received fluorouracil in combination with leucovorin. (p. 526, left column fourth paragraph, right column first paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to coadminister the fluorouracil-containing compositions of Klysov et al. with leucovorin, to a patient having colon cancer. One of ordinary skill in the art would have been motivated to combine these two elements because Jakobsen et al. specifically discloses that 5-fluorouracil can be productively co-administered with leucovorin for treating colon cancer. One of ordinary skill in the art would reasonably have expected success because combining two elements known in the prior art to be useful for treating the same condition is well within the ordinary and routine level of skill in the art.

Therefore the invention taken as a whole is *prima facie* obvious.

The applied reference has a common assignee and one common onventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be

overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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